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NEW POLYMERS AND APPLICATIONS

The present invention relates to a novel class of polymers, macro aggregates formed by said polymers, and various uses of said polymers and aggregates for controlled release of substances.

Background of the Invention

Polymers are a versatile class of materials that offer numerous benefits compared to other material groups. Polymer structures have also been used to facilitate solutions to a variety of biomedical problems. Remarkable properties such as biocompatibility and/or biodegradability, have been the reasons why they have been used in, for instance, sutures and bioactive membranes. Promising future applications involves areas such as platforms for tissue regeneration, stent coatings, replacement materials for eye lenses and various cosmetic solutions.

Another application is the growing need for new sophisticated and "smart" materials for active drug delivery. Controlled drug delivery technology represents one of the most advanced areas, and the need for controlled release systems is high. Such delivery systems offer numerous advantages compared to conventional dosage forms, including improved efficacy, reduced toxicity and improved patient compliance and convenience. Such systems often use synthetic polymers as carriers for the drugs. Although the introduction of the first clinical controlled release systems occurred less then 25 years ago, 1997 sales of advanced drug delivery systems in the United States alone were approximately $14 billion dollars.

The methods of controlled release are generally divided into two classes; temporal control and distribution control. In temporal control, drug delivery systems aim to deliver the drug over an extended duration or at a specific time during treatment. In distribution control, drug delivery systems aim to target the release of the drug to the precise site of activity within the body. The two methods have distinct differences, and in every situation there is a certain need that can be fulfilled depending on the choice of release system.

In connection with this development, the need for materials with new biomedical functions have increased, and new areas in which the use of polymers has been introduced are, for instance, bone implant replacements, drug delivery vectors, sutures, and tissue engineering.

In order to establish working platforms suitable for either temporal or distribution control release systems, the use of polymers have been widely used. Many polymer classes have been used, including polyesters, polyorthoesters, polyanhydrides, phosphorous containing polymers, and polyamides. Moreover, numerous examples of hydrophobic/hydrophilic block copolymers with surfactant properties have also been made. One example is the polylactic acid (PLA) polyethylene glycol (PEG) copolymer system in which the PEG chain adds hydrophilic properties whereas the PLA chain is hydrophobic, the whole structure being biodegradable.

The research groups of Nakabayashi and Ishikara have developed a new type of copolymer in which a hydrophobic polymer has been used in combination with hydrophilic phosphatidyl choline units. By doing so, a new biocompatible amphiphilic structure was created. To mention a few copolymer systems developed by Nakabayashi *et al* are various polymethacrylates, polysulfones, polyethylenes and polystyrenes, which have been used in combination with phosphatidyl choline units. Some of the most significant improvements compared to the homopolymer have been increased blood compatability and reduced plasma protein adsorption. These effects have been studied in membranes and surfaces as well as in particles (micelles). In all studies a stable, non-degradable polymer was used in combination with phosphatidyl choline. Since the first published data was released in the early 90's, many other research groups have contributed to further research in the area.

Thus, over the last two to three decades there has been a development of controlled release systems for medical use. Numerous patents have been filed and granted on such systems. These systems have been based on various kinds of structures, such as micelles, vesicles, surface bound agents, etc.

A phenomenon often observed with controlled release formulations of medicinal products is that of the "burst effect", that is, a very large initial release of the active substance. In certain cases, this effect may be desirable. On the other hand, there are cases where it may prove to be dangerous. This is the case, which is particularly detrimental to hormone therapies, which use active principles having very troublesome or even toxic side effects in high concentrations. In such cases, it is imperative to be able to ensure slow and uniform release in small quantities of the active principle.

Attempts to overcome such effects have been made, see e.g. US-6,319,512. The invention claimed in this patent provides an implant for the controlled release of at least one pharmaceutically active agent, said implant comprising a core which contains at least one active agent and a sheath which surrounds said core, and is wherein said sheath is composed of at least one polymeric film applied around said core. According to a preferred embodiment of that invention, the sheath is composed of at least two polymeric films, one surrounding part of the core and the other surrounding the remaining part. This is however, a fairly complex structure, requiring fairly complex manufacturing, and thus has disadvantages in terms of manufacture cost.

As already indicated, during the last decade polymer research has been driven towards the design of materials with multiple properties. This includes both new polymerization techniques as well as the use of polymers in combination with other highly ordered and controlled structures. The development of dendritic, hyper branched and star-like structures parallel to advances in ring-opening metathesis (ROMP), atom transfer radical (ATRP) and ring-opening (ROP) polymerization techniques have enabled the preparation of well-defined functional polymeric materials with predictable molecular weights and narrow polydispersities. This development has enabled the synthesis of a variety of new architectures developed from a number of different building blocks. Many of these have been proven successful; however, a biodegradable slow release system with bio-mimicking and non-thrombogenic properties has not yet been developed.

Summary of the Invention

Thus, in view of the need for new materials suitable for controlled release of e.g. medicaments having biodegradable and biocompatible properties, the object of the invention is to make available a biodegradable, biocompatible polymer that is capable of forming particles (micelles), vesicles, surfaces and membranes, and other structures in which a biologically active agent, e.g. a drug, can be incorporated in such a way that its release to the host can be controlled to a high degree of accuracy.

This object is achieved in a first aspect of the invention by a novel polymer compound as defined in claim1.

In a further aspect there is provided a macromolecule in the form of a dendrimer or comb-co-polymer structure based on the polymer defined in claim 1. This macromolecule is defined in claim 2.

There is also provided, in a third aspect of the invention, a vehicle for the controlled release of biologically active agents, e.g. drugs, said vehicle being defined in claim 13. Preferred forms of said vehicle in the form of micelles, vesicles, membranes, and surfaces are defined in the claims depending from claim 13.

Finally, there is also provided a method of making the polymer and polymer aggregates, the method being defined in claim 18.

The present invention polymers have several advantages for use in systems for controlled drug release. One advantage is that, in the present invention the polymers are compatible with blood, a property imparted by phosphatidyl choline. The polymer is also biodegradable. Moreover, the combination of hydrophilic and hydrophobic segments of the material gives the present invention polymers the appropriate physical properties needed to form particles or membranes. In addition, the high level of synthetic control also leads to perfect control of functionality, thereby increasing the flexibility of this new polymer material, i.e. this material makes it possible to incorporate various types of drugs. With the present invention and the accompanying technique for ring-opening polymerization of cyclic esters, it is

possible to tailor the length of the polymers or in a later step the size of particles, depending on the application. Particle or membrane formation can be achieved either by self-assembly of linear polymers, or alternatively, by a dendritic approach in order to form a "one molecule-one particle" type of system.

Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

Brief Description Of The Drawings

The present invention will become more fully understood from the detailed description given hereinbelow and the accompanying drawings which are given by way of illustration only, and thus not limitative of the present invention, and wherein

Fig. 1 illustrates the synthetic route for terminated poly ε-caprolactone – phosphatidyl choline according to the present invention.

Fig. 2 illustrates micelle formation of an amphiphilic molecule according to the present invention.

Fig. 3 shows an example of a dendrimer structure, a branched polyfunctional one particle molecule, according to the present invention

Fig. 4 exemplifies other cyclic esters that, in addition to ε-caprolactone, that could be used to synthesise the polymer according to the present invention.

Detailed Description of Preferred Embodiments

The approach has been to combine the use of phosholipid moieties in combination with biodegradable polyesters in order to prepare a fully biocompatible and biodegradable polymer system. One major goal has been to design macromolecules so they form a certain type of structure depending on the application. Two examples are membranes and micelles.

The present invention provides polymer compounds comprising at least one biodegradable polyester having a terminal functional group based on the hydrophilic moiety in phospholipid.

The polymer compounds according to the present invention can be aggregated and have the shape of micelles, vesicles and membranes. The polymer compounds can also be designed such that they emanate from a central core so as to form a dendrimer. The dendrimer-type of polymer compound forms an essentially spherical particle with said functional groups forming the surface layer of said spherical particle or is concentrated at the surface, thus mimicking the surface of vesicles.

A solution of the micelles or spherical particles formed by the polymer compound according to the present invention can be used as a drug formulation, where the micelles or particles enclose a medicament.

The polymer compound according to the present invention can further be used for coating an object, e.g. a vehicle, and the thus formed coating may be loaded with an (biologically) active agent, e.g. a drug. The coating constitutes a layer having a thickness of 0.1-100 μm, said functional groups forming an outer layer of said coating.

The coated object may be used in biological or medical applications, such as a medical device, medical device for implantation, stent, artificial orthopedic device, spinal implant, joint implant, attachment element, bone nail, bone screw, or a bone reinforcement plate.

The biodegradeable polyester used in the polymer compound according to the present invention is polymerized from a cyclic monomer selected from the group of cyclic esters including ε-caprolactone, lactide, glycolide, β-butyrolactone, propiolactone and combinations thereof.

The terminal functional group of the polymer compound according to the present invention is positively or negatively charged, or is zwitterionic or electrically neutral.

The terminal functional group is selected from but not restricted to phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, ammonium salt, carboxylic acid or carboxylate, phosphonic acid, phosphate, phosphonate, sulphonate, sulphonic acid, peptide, nucleotide, carbohydrate.

The molecular weight of the polymer compound according to the present invention can be in the range 1000 – 200 000 g/mol, preferably 20 000 g/ mol. The present invention also provides a method of preparing a biodegradable and biocompatible polyester having a terminal functional group based on a phospholipid, which is comprised by the following steps: reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/an initiator to provide a ring opened polymer having an –OH terminal end; reacting the –OH terminal end of the obtained polymer with a phosphorous containing compound to provide a polymer having a phosphate terminated polymer; and reacting said phosphate terminated end of said polymer to obtain a polymer having functionalized end.

The phosphorous containing compound in said method is preferably selected from the group consisting of ethylene chloro phosphates. In said method, the step of providing a functionalized polymer also comprises reacting the terminal end with trimethylamine. The resulting polyester is preferably poly ε-caprolactone–phosphatidyl choline.

The present invention further provides a method of preparing biodegradable and biocompatible polyester amphiphiles having a charged terminal functional group, the method comprising the following steps: reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/initiator to provide a ring-opened polymer having an –OH terminal end; and reacting said –OH terminal end of the obtained polymer with a ω-halo acid halide to obtain an alkyl halide; and reacting said polymer/ polymers to obtain a polymer having a functionalized end.

In said method, the step of providing a functionalized polymer comprises reacting the terminal end with trimethylamine. The resulting polyester is preferably poly ε-caprolactone–ammonium salt.

The present invention further provides a method of preparing a biodegradable and biocompatible polyester amphiphiles having a charged terminal functional end, comprising the steps of reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/an initiator to provide a polymer having an –OH terminal end; reacting the –OH terminal end of the obtained ring-opened polymer with a succinic anhydride to produce a functionalized (carboxylic acid)- or carboxylate-terminated polymer.

In said method, the step of providing a functionalized polymer comprises reacting the terminal end with derivatives of carboxylic acid or its anhydrides. The resulting polyester is preferably poly ε-caprolactone–carboxylic acid or poly ε-caprolactone–carboxylate.

Now the general experimental methods will be described.

Tin(II)trifluoromethane sulfonate ($Sn(OTf)_2$) was purchased from Aldrich and was azeotropically distilled with toluene prior to use. ε-caprolactone (ε-CL) and triethylamine were purchased from Aldrich and were distilled over calcium hydride prior to use. Acetonitrile was purchased from Lancaster and was distilled from magnesium sulfate prior to use. Ethylene chloro phosphate was purchased from Lancaster and was used as received. Ethanol was purchased from Kemetyl and was distilled over calciumhydride prior to use. ^{1}H-NMR was performed on a Varian 200 MHz. SEC was performed on a Waters instrument.

The following section will be based on **Figure 1**, which illustrates the synthetic route for terminated poly ε-caprolactone – phosphatidyl choline.

Synthesis of poly ε-caprolactone, PCL (step **1** in **Figure 1.**)

To a nitrogen flask was added a stirbar and the flask was sealed with a septum. The equipped flask was carefully flame-dried under vacuum and purged with nitrogen. The reactants were then syringed in under nitrogen. First the catalyst stock solution (0.01 mol% to initiator) and the initiator alcohol (0.583 mmol for

DP=30) were added (**II**) and stirred for approximately 20 minutes. 2.0 g (17.5 mmol) of ε-caprolactone (**I**) were then added and the flask was brought to 35°C. The mixture was stirred vigorously and when the reaction was finished, the crude poly ε-caprolactone (PCL, **III**) mixture was dissolved in 40 mL THF and precipitated in 250 mL of cold hexanes. The precipitate was filtered and washed 3 times with 20 mL of hexanes. The filtrate was dried in vacuum at 40°C until a constant weight was reached in order to determine the yield of the reaction. Molecular weights and polydispersities were determined with ^{1}H-NMR (Nuclear Magnetic Resonance) and SEC (Size Exclusion Chromatography).

Synthesis of PCL coupled to ethylene chloro phosphate (step **2** in **Figure 1**)

2.0g (1.10mmol) of PCL with a molecular weight of 1824 g/mol (DP=16) was weighed in a pre-dried two-neck round-bottom flask and dissolved in 20mL dry THF. Two equivalents of dry triethylamine (0.31mL, 2.19mmol) were thereafter added under protecting nitrogen gas. The flask was attached to a dropping funnel and cooled to -10°C. An additional 10mL of dry THF and 0.15mL (1.64mmol) of ethylene chloro phosphate (**IV**) was added. The solution was slowly added drop wise and the solution was stirred for approximately 3 hours. During the course of the reaction a white triethyl ammonium chloride salt precipitated from the solution. After the reaction was completed the solution was filtrated to remove the main fraction of the triethyl ammonium chloride salt. Thereafter the solution was precipitated in cold methanol yielding a white ethylene phosphate terminated PCL (**V**). The compound was allowed to dry in a vacuum oven at 40°C until constant weight.

Synthesis for the ring-opening of ethylene phosphate to yield phosphatidyl choline terminated PCL (step **3** in **Figure 1**)

0.5g (0.25mmol) of a ethylene phosphate terminated PCL (DP = 16) was weighed in a 50mL pre-dried round-bottom flask and thereafter dissolved in 10mL of dry acetonitrile. The solution was transferred to a pressure tube with two stopcocks, purged with nitrogen and sealed, thereafter cooled to -20°C. Two equivalents (0.50mmol, 47μL) of trimethylamine$_{(g)}$ to the PCL polymer was condensed into the pressure tube and thereafter slowly heated to 60°C. The pressure tube was left

under stirring for 5 hours and then left to heat to ambient temperature. Following ring-opening residuals of acetonitrile was removed by rotational evaporation to produce PCL-phosphatidyl choline (**VI**) as a white powder.

Results

The emphasis was to synthesise a fully biodegradable polymer in combination with phosphatidyl choline as a possible future carrier for controlled drug release or other biomedical applications. The ambition has been to introduce the use of phospholipid analogues into new areas of polymer research, keeping in mind what already has been done in this area. With the recent development of polymerisation techniques for the synthesis of biodegradable polyesters it is not until now that this has been possible. Controlled ring-opening polymerisation of for instance lactides and ε-CL now makes it possible to design polyesters with controlled molecular weight and narrow polydispersities. It should also be pointed out that by the approval from the food and drug administration (FDA), both PCL and PLA are classified as biocompatible polymers, which degrades into molecules acceptable in the human metabolism.

In our initial results a series of various linear PCL with various molecular weights was made, mainly to demonstrate the high level of control in this synthetic route, but also to create the first amphiphiles with particle or membrane forming properties. The following table recall some initial polymerisation data.

Table 1: Ring-opening polymerisation data of PCL.

Sample	Catalyst	Initiator	Temp. [°C]	Time [hrs]	Yield [%]	I / M Ratio	DP	PDI
1	$Sn(OTf)_2$	EtOH	35	4	70	5	5	1,14
2	$Sn(OTf)_2$	EtOH	35	15	90	15	17	1,18
3	$Sn(OTf)_2$	EtOH	35	20	95	30	27	1,07
4	$Sn(OTf)_2$	EtOH	35	39	97	60	66	1,19

From **Table 1** it is clear that the molecular weight of PCL can be controlled by the ratio of initiator to monomer, as previously explained. Using ^{1}H-NMR analysis the PCL was fully characterized and both the α- and the ω-end groups were identified. The following chemical shifts were observed for the PCL molecule initiated from ethanol: ^{1}H-NMR ($CDCl_3$) δ = 1.23 (t, α-end, CH_3-), 1.30-1.42 (m, poly, -CH_2-), 1.55-1.69 (m, poly, -CH_2-), 2.29 (t, poly, CHO_2-), 3.63 (t, ω-end, -CH_2OH), 4.04 (t, poly, -CH_2CO-), 4.11 (q, α-end, -CH_2-).

The characterisation in the following coupling step was also performed using NMR analysis. From the obtained spectra an additional multiple between δ = 3.68 – 3.90 ppm from the ethylene proton signals in ethylene phosphate was observed, however overlapping the ω-end group of the PCL. To a certain complete conversion and formation of only the desired compound, a model reaction for the coupling step was performed. Instead of PCL, a poly (D,L)-lactide was used, in order to observe the resonance from the phosphate reagent, without any influence from the polymer. This model was chosen since it contained no new steps throughout the synthesis, oppositely it tracked every step using PCL. ^{1}H and ^{13}C were used to characterise the obtained products and the following shifts were observed:
^{1}H-NMR, $CDCl_3$ δ = 1.23 (t, 3H, $C\underline{H}_3CH_2$-), 1.42 (d, 3H, -CH-$C\underline{H}_3$), 1.53 (poly, -CH-$C\underline{H}_3$), 3.65 – 3.85 (m, 4H, -O-$C\underline{H}_2$-$C\underline{H}_2$-O-), 4.18 (q, 1H, -$C\underline{H}$-CH_3), 4.33 (q, 2H, $CH_3C\underline{H}_2$-), 5.15 (poly, -$C\underline{H}$-CH_3)
^{13}C-NMR, $CDCl_3$ δ = 14.1, 16.7, 20.53, 61.6, 66.8, 69.0, 69.3, 169.5, 169.7
The observed results in the model reaction support the obtained data from the PCL-ethylene phosphate NMR.

In the last ring-opening step, the final PCL phospatidyl choline molecule was also characterised with ^{1}H-NMR. A distinct singlet from the methylene signals in the choline unit was observed at 2.82 ppm. This step was also performed on the model reaction using poly (D,L)-lactide, which contained the choline resonance at the same frequency. In addition, it gave supporting information that otherwise would not have been observed. The ethylene protons in the phosphatidyl unit are now separated at 3.85 ppm and at 4.04 ppm. In PCL the polymer peak obscures the

signal at 4.04ppm. From the NMR results, it is clear that the synthetic route is functioning.

Following the synthesis two particle formation experiments were performed, mainly to get an indication on how these structures behaved. Particle formation using two different routes was conducted.

Using the first route, a phosphatidyl choline terminated PCL (DP=16) was dissolved in chloroform ($CHCl_3$). Thereafter the dissolved compound was added drop wise to water. Well-defined drops were formed (two-phase system). Following addition, a stir bar was added and stirring was applied for approximately 30 minutes, creating a fine-dispersed particle solution. In the early stage, after the stirring had been stopped, flocculation was observed. However, after 30 minutes of stirring only stable particles were obtained. By "stable" it is meant that no visual flocculation occurred, indicating stable particles. Environmental – Scanning Electron Microscopy (E-SEM) analysis indicated particles with a diameter of 1-10 μm. Evaporation of the chloroform solidified the particles.

Using the second route, a solvent combination was chosen that could allow a single phase of a combination of the solvents but with the PCL-phosphatidyl choline being totally soluble in one. An acetone-water combination was chosen (5mL / 95mL) and a small amount (10 mg) of the PCL (DP=16)-phosphatidyl choline. At first the compound was dissolved in acetone, and was thereafter added drop wise into water. After the addition, the solution was perfectly transparent, indicating particle sizes in the nanometer (nm) range.

These two experiments gave an indication on that particle formation is possible and that the system is surface-active. The desired effect is seen in **Figure 2**, which shows the micelle formation of the amphiphilic molecule.

In **Figure 2** the rings represent hydrophilic phosphatidyl choline units whereas the zigzag lines represent hydrophobic PCL chains. The figure schematically shows the self-assembly of these molecules in an aqueous medium.

To extend the use of this synthetic route, one can also include non-linear type of molecules. In a totally branched system, e.g. initiated from a polyol or macro initiator, one could obtain a "one-molecule-one-particle" system, in which the self-assembly from many molecules has been changed into a "one-molecule-one-particle" forming system with a controlled size. Dendritic type of structures could for instance be synthesized from the coupling of benzylidine protected bis(hydroxymethyl) propionic acid (bis-MPA) with benzyl protected bis-MPA followed by selective deprotection to yield a first generation dendrimer. An alternative approach would be the tailoring of dendritic structures from benzylidene protected glycerol and 2-bromopropionic acid. The addition of branching points in combination with ring-opening polymerization gives an almost unlimited source of architectural possibilities, and the common link is that the functionality on the surface will be much higher compared to linear structures. The hydrophobic unit would still be biodegradable polyester, and the phopshatidyl choline unit imparting hydrophilic properties. One change is the architecture of the molecule, i.e. the branching points, which yield a molecule with a much higher functionality on the surface. The end-functionality, however, does not always have to be phosphatidyl choline; other functionalities or combinations of functionalities can also be chosen as well as the addition of for example receptor ligands. With this synthetic approach, structure, size and functionality can be controlled. One visual example of such a structure is a branched polyfunctional one particle molecule, as seen in **Figure 3** (please observe that the rings could mean an end group which is not phosphatidyl choline).

The monomer used in the previously described synthetic routes has in all cases been ε-CL. Recently, the controlled ring-opening polymerization of other cyclic esters has been investigated, and it is now possible to tailor the molecular weight of other polyesters as well. A summary of other cyclic esters, which either separately or in combination, could be used in the described synthesis, is shown in **Figure 4.** In all cases the, obtained polyester is biodegradable.

Thus, according to the present invention, a fully biodegradable polyester-phosphatidyl choline compound was synthesized using highly developed polymerization techniques. This molecule had amphiphilic behavior due to hydrophobic properties from the PCL chain and hydrophilic properties from the phosphatidyl choline unit. A model reaction was used to more clearly demonstrate the coupling step between PCL and ethylene phosphate. PCL is one example of a biodegradable polyester, but according to the present invention other monomers, such as lactides, could also be used to produce similar structures. In the present invention synthetic route, only a linear type of molecules was created, but it is also possible to provide branched/dendritic type of structures with a much higher functionality on the surface. The polymers according to the present invention can suitably be used in biological and medical applications, for instance as membranes and as drug delivery vectors.

With the invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Claims

1. A polymer compound, comprising at least one biodegradable polyester having a terminal functional group based on hydrophilic moieties of phospholipids.

2. A polymer compound as claimed in claim 1, comprising a plurality of biodegradable polymers emanating from a central core so as to form a dendrimer.

3. Aggregate of polymers as claimed in claim 1, having the shape of micelles, vesicles and membranes.

4. A polymer compound as claimed in any of claims 1-3, wherein said polyester is polymerized from a cyclic monomer.

5. A polymer compound as claimed in claim 4, wherein said cyclic monomer is selected from the group of cyclic esters.

6. A polymer compound as claimed in claim 5, wheren said cyclic esters are selected from the group consisting of ε-caprolactone, lactide, glycolide, β-butyrolactone, propiolactone and combinations thereof.

7. A polymer compound as claimed in claim 1-6, wherein the terminal functional group is positively charged.

8. A polymer compound as claimed in claim 1-6, wherein the terminal functional group is negatively charged.

9. A polymer compound as claimed in claim 1-6, wherein the terminal functional group is zwitterionic or electrically neutral.

10. A polymer compound as claimed in claim 1-9, wherein the terminal functional group is phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl

serine, ammonium salt, carboxylic acid or carboxylate, phosphonic acid, phosphate, phosphonate, sulphonate, sulphonic acid, peptide, nucleotide, carbohydrate.

11. A polymer compound as claimed in claim 1-10, the molecular weight of which is in the range of 1000 – 200 000 g/mol, preferably 20 000g/mol.

12. A dendrimer type polymer compound as claimed in claim 2, forming an essentially spherical particle with said functional groups forming the surface layer of said spherical particle.

13. An object provided with a coating made of a polymer compound as claimed in claim 1, wherein said polymer compound forms a layer having a thickness of 0.1 – 100 µm, said functional groups forming an outer layer of said coating.

14. The object as claimed in claim 13, wherein said coating is loaded with an (biologically) active agent.

15. The object as claimed in claim 13 or 14, wherein the object is an object used in biological or medical applications.

16. The object as claimed in claim 15, wherein it is a medical device, medical device for implantation, stent, artificial orthopedic device, spinal implant, joint implant, attachment element, bone nail, bone screw, or a bone reinforcement plate.

17. A drug formulation, comprising a solution of micelles or spherical particles formed by a polymer compound as claimed in claim 1, wherein the micelles or particles enclose a medicament.

18. A method of preparing a biodegradable and biocompatible polyester having a terminal functional group based on a phospholipid, the method comprising the following steps:
-reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/an initiator to provide a ring opened polymer having an –OH terminal end;

-reacting the –OH terminal end of the obtained polymer with a phosphorous containing compound to provide a polymer having a phosphate terminated polymer; and

-reacting said phosphate terminated end of said polymer to obtain a polymer having functionalized end.

19. The method as claimed in claim 18, wherein said phosphorous containing compound is selected from the group consisting of ethylene chloro phosphate.

20. The method as claimed in claim 18 or 19, wherein the step of providing a functionalized polymer comprises reacting the terminal end with Me_3N.

21. The method as claimed in any of claims 18-20, wherein the resulting polyester is poly ε-caprolactone–phosphatidyl choline.

22. A method of preparing biodegradable and biocompatible polyester amphiphiles having a charged terminal functional group, the method comprising the following steps:

-reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/an initiator to provide a ring-opened polymer having an –OH terminal end;

-reacting said –OH terminal end of the obtained polymer with a ω-halo acid halide to obtain an alkyl halide; and

-reacting said polymer/ polymers to obtain a polymer having a functionalized end.

23. The method as claimed in claim 22, wherein the step of providing a functionalized polymer comprises reacting the terminal end with Me_3N.

24. The method as claimed in claim 22 or 23, wherein the resulting polyester is poly ε-caprolactone–ammonium salt.

25. A method of preparing a biodegradable and biocompatible polyester amphiphiles having a charged terminal functional end, the method comprising the following steps:

-reacting a cyclic ester monomer and an alcohol in the presence of a catalyst/an initiator to provide a polymer having an –OH terminal end; and
-reacting the –OH terminal end of the obtained ring-opened polymer with a succinic anhydride to produce a functionalized (carboxylic acid)- or carboxylate-terminated polymer.

26. The method as claimed in claim 25, wherein the step of providing a functionalized polymer comprises reacting the terminal end with derivatives of derivatives of carboxylic acid or its anhydrides.

27. The method as claimed in claim 25 or 26, wherein the resulting polyester is poly ε-caprolactone–carboxylic acid or poly ε-caprolactone–carboxylate.

Abstract

The present invention provides a biodegradable, biocompatible polymer that is capable of forming particles (micelles), vesicles, surfaces and membranes, and other structures in which a biologically active agent, e.g. a drug, can be incorporated in such a way that its release to the host can be controlled to a high degree of accuracy. The present invention provides polymer compounds comprising at least one biodegradable polyester having a terminal functional group based on hydrophilic moieties from a phospholipid.

Fig. 1

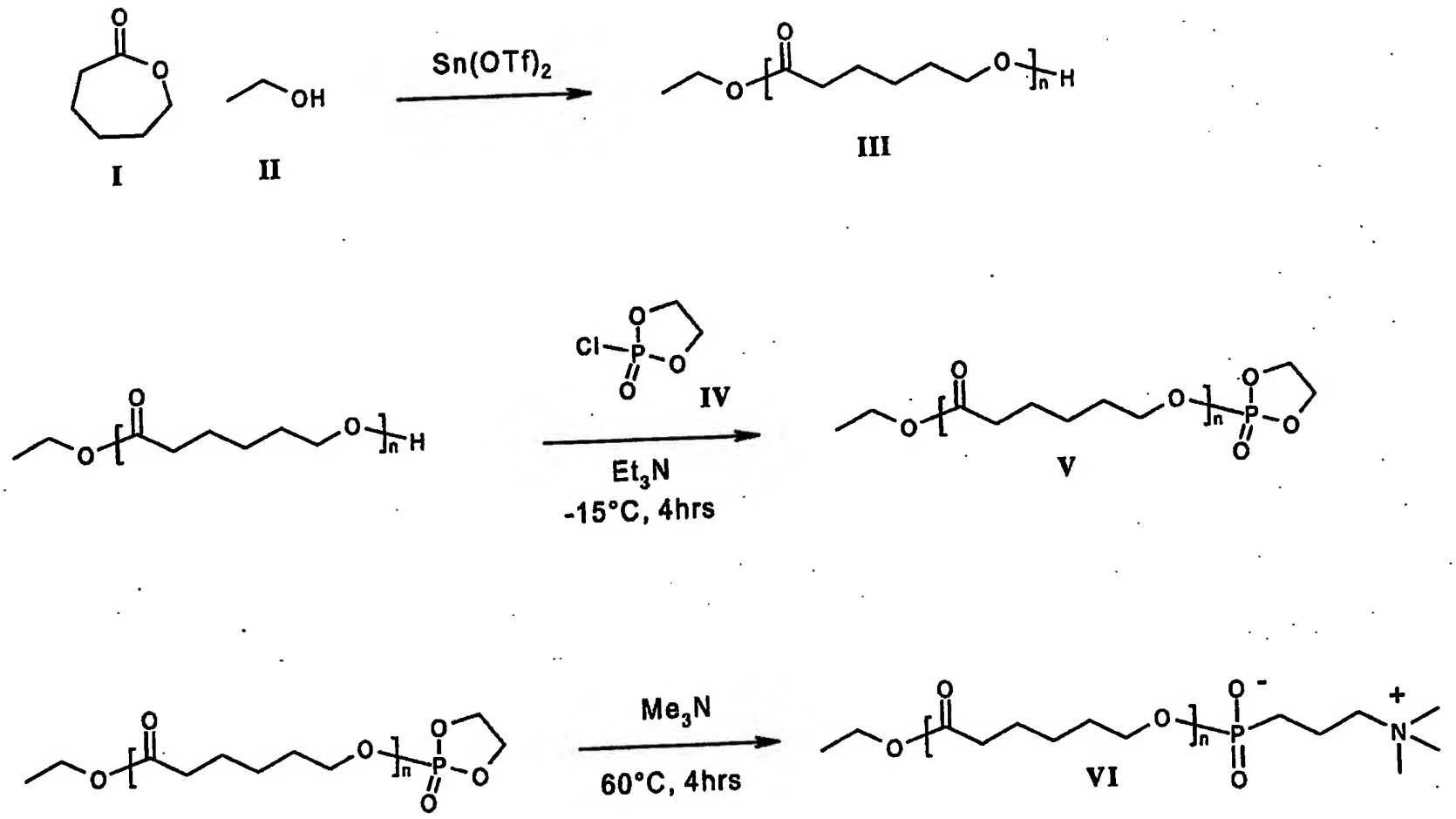


Figure 1

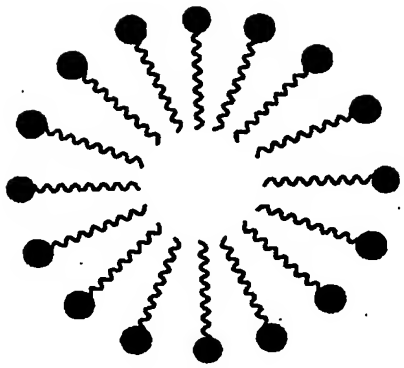


Figure 2

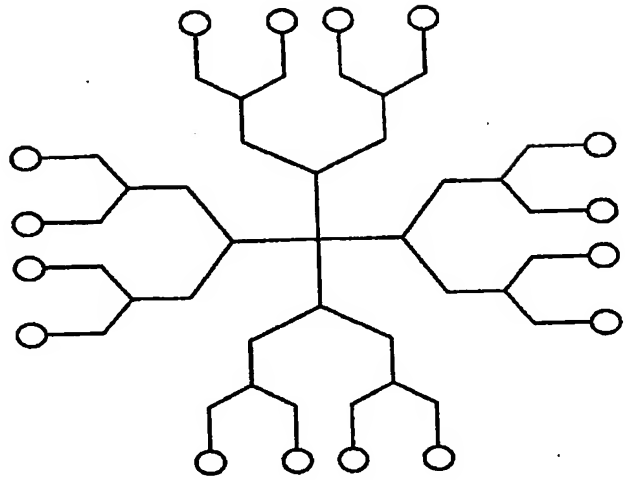
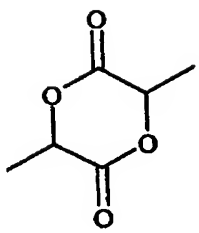
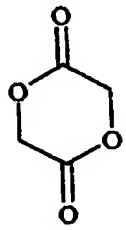


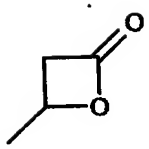
Figure 3



Lactide



Glycolide



β-butyrolactone

Figure 4